UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/348,354	07/07/1999	MENZO HAVENGA	4123US	5117

7590 03/26/2003

ALLEN C TURNER
TRASK BRITT & ROSSA
PO BOX 2550
SALT LAKE CITY, UT 84110

EXAMINER	
MARVICH, MARIA	
ART UNIT	PAPER NUMBER
1636	26

DATE MAILED: 03/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/348,354	Applicant(s) HAVENGA ET AL.	
	Examiner Maria B Marvich, PhD	Art Unit 1636	

-- Th MAILING DATE of this communication appears on th cover sh et with th correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *13-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,3, 9-11 and 33-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This office action is in response to an amendment and a Request for Continued Examination filed 1/6/03. Claims 49 and 50 have been added. Claims 2, 33, 35, 37, 40, 43 and 46 have been amended. Claims 12-32 are drawn to non-elected inventions and have been withdrawn from consideration. Claims 1-3, 9-11 and 33-50 are pending in this application.

It is indicated in the amendment filed 1/6/03 that claims 1 and 9-11 have been cancelled with the Amendment filed on 2/28/02. In the amendment filed 2/28/02, the claims are indicated as canceled on the marked up version but not on the clean version. The clean version of the amendment is entered into the case, the marked up version is for the convenience of the examiners and is not entered. In the amendment filed 1/15/03, the claims are indicated as cancelled in the remarks. This is an erroneous indication of claim cancellation. The claims need to be canceled by amendment (see MPEP 714).

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotides and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). Specifically, there are sequences disclosed in figures 7 and 10 and table 3 that do not have SEQ ID numbers associated with them. Please identify the sequences by SEQ ID NO:.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 9-11 and 33-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Crystal et al. (US patent 6,127,525) in view of Wickham et al. (WO 96/26281). **This rejection is maintained for reasons of record in Paper No. 27 and reiterated below.**

Applicants claim a recombinant adenovirus comprised of a recombinant capsid comprised of a chimeric fiber protein encoding the gene sequence encoding the part of a fiber protein adapted to exhibit a desired tropism to a plurality of target cells in a host and fused to a tail region of a fiber of the adenovirus serotype from which the recombinant vector was derived and vectors and methods for producing said recombinant adenovirus.

Crystal et al. teach a chimeric adenoviral coat protein (particularly a chimeric hexon and/or fiber) that has a decreased ability to be recognized by a neutralizing antibody or a decreased antigenicity (abstract). Crystal et al. further teach that the adenovirus coat proteins can be modified by deleting and replacing a region of the coat proteins (e.g. a penton, hexon and/or

fiber protein) with the corresponding region from another adenoviral serotype i.e. Ad 1, 2, 3, 5, 6, 7, 11, 12, 14, 16, 21, 34, 35, 40, 41 or 48 (column 4, line 32-41). Crystal teaches that restriction sites can be used to introduce or remove DNA sequences (column 14,line 15-19). The chimeric coat protein gene sequence is inserted into the vector using the restriction sites (column 17, line 62-66). Crystal et al. teach a method of producing a chimeric adenovirus with a transfer vector such as an adenoviral vector comprising a chimeric coat protein wherein a vector comprising sequences from the adenoviral left arm and a vector comprising sequence from the adenoviral right arm are introduced into a packaging cell such as 293 cells to generate a recombinant vector that comprises a portion of each of the vectors (column 18).

Crystal et al. do not explicitly teach the limitation that the chimeric fiber protein will also be responsible for exhibiting a desired tropism.

Wickham et al. teach the construction of adenoviral fiber proteins and methods of their use for altering the tropism of adenoviral vectors for gene therapy. Wickham teaches chimeric fibers that are comprised of nonnative amino acid in addition to or in place of a native fiber amino acid sequence sequences (page 9, line 1-10). By nonnative is meant any sequence that is not found in the native fiber of a given serotype of adenovirus for example an Ad3 fiber amino acid sequence expressed in an Ad 5 chimeric fiber protein (page 9, line 28-37). Wickham teaches that there is a high degree of similarity between the fiber molecules of the more than 41 human serotypes of adenovirus so that any one of the serotype of human or nonhuman adenovirus can be used (page 13, line 16-20). Wickham et al. teach that one can advantageously practice the claimed invention by utilizing restriction sites within the native fiber coding

sequence to incorporate various different nonnative receptor or protein binding domains into the chimeric fiber proteins Examples 1-2, column 7, lines 37-61).

Wickham does not teach that the chimeric fibers also exhibit altered antigenicity.

It would have been obvious of ordinary skill in the art at the time of applicants' invention to practice the methods taught by Crystal et al. for construction of adenoviral gene transfer vectors comprising a chimeric fiber and chimeric hexon with chimeric fibers comprising an amino terminal fiber region from a first serotype and a tropism-determining domain (i.e. the "receptor-binding" domain according to Wickham et al. derived from an adenovirus of a different serotype because Crystal et al. teach it is within the skill of the art to develop and use adenoviral constructs comprising hexon and fiber proteins and Wickham et al. teach it is within the skill of the art to construct and use chimeric fiber proteins having a receptor binding domain obtained from an adenovirus of a second serotype. A person of ordinary skill in the art would have been motivated to utilize the teachings of Wickham et al. to design a chimeric fiber of Crystal et al. such that the resultant fiber incorporated the altered tropism as taught by Wickham with the altered antigenicity as taught by Crystal in order to receive the expected benefit of being able to efficiently interchange different receptor-binding domains from adenoviruses of different serotype, as taught by Wickham et al, so as to easily and rapidly alter the tropism of the adenoviral vectors taught by Crystal et al. Given the teachings of the cited art and the level of skill of the ordinary skilled artisan at the time of the applicant's invention, it must be considered that said ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 9-11 and 33-50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **THIS IS A NEW MATTER REJECTION**.

Applicants claim a part of a fiber protein fused to **a tail region** of a fiber of the adenovirus serotype from which the recombinant vector was derived or from the first adenovirus serotype. Pages 32-41 of the specification are cited as support (in the Havenga II Declaration filed 1/6/03) for the limitation that the native tail fiber is retained. Pages 32-41 teach that the sequences from 19 different serotypes of adenovirus were aligned to identify the conserved region in the tail and known regions. From the alignment, degenerative oligonucleotides were generated and used to amplify the fiber sequences. The oligonucleotides used to amplify the specific tail regions are listed in table 3. The fiber DNA's were then amplified, digested and inserted into pBr/AdBAMRΔΔFib. There is no support in this disclosure that the tail region of the native adenovirus fiber protein is retained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-3 and 33-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2, 33, 35, 37, 40, 43, 46, 49 and 50 are vague for reciting "derived from". It is unclear how closely related the derived sequences are to the original adenovirus and it is also unclear what the functional and structural relationship between the original adenovirus and those "derived from" said adenovirus are. The metes and bounds of the claimed subject are unclear.

The meaning of " functionally inserting" in claims 2, 43 and 46 is unclear. Does applicant mean that the insertion must be functional or that the insert must be functional or is something else intended by this language?

Claims 37 and 40 are vague in reciting "a functional part of a penton or hexon protein" or "a functional part of a fiber protein". The metes and bounds of the claimed subject matter are unclear as the functional and structural requirements of the "functional part" are unknown.

Claim 40 is unclear for reciting "the method comprising: the fiber protein adenovirus serotype 35". While the fiber protein can be used in the method steps, it is not itself a method step.

Claim 50 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: how a chimeric adenoviral particle can be "provided" with a gene sequence encoding a tail region.

Response to Arguments

On pages 6-13, applicant traverses the rejections under 35 U.S.C. 103(a) over Crystal et al. in view of Wickham et al.. Applicant argues that the proposed references do not teach making chimeric fiber proteins. Instead, Crystal et al. generate a chimeric capsid comprised of an Ad5 penton base and an Ad7 fiber. While chimeric fiber proteins may be envisioned, chimeric fiber proteins comprising the tail region of the native fiber fused to a part of the fiber from a second serotype are not specifically taught. Applicant further argues that the teachings of Wickham do not cure the failure of the Crystal reference to teach every limitation of the instantly claimed invention. Wickham teaches generation of Ad5/Ad2 and Ad5/Ad3 chimera whereas the applicants specifically claim superior chimeras in which the second serotype of adenovirus is from serotype groups 11, 14, 16, 21, 34, 35 and 50. Applicant cites the Havenga Declaration II, addressed below, as support that the vectors and adenovirus of the instant invention are superior to that of the Crystal or Wickham invention.

Applicant further argues that no proper suggestion or motivation has been identified to combine the reference teachings. Applicant contends that reliance on the level of skill in the art for the suggestion or motivation is not a proper basis for *prima facie* obviousness. Despite the reasonable expectation of success and the readily recognized advantages of combining the teachings, "the office nevertheless must show a teaching or suggestion or motivation in the cited references that would lead an ordinarily skilled artisan to select and combine reference teachings" (page 12 end to top page 13). Finally, applicant argues that Crystal teaches away from the instant invention by teaching that effective reduction in immune responses cannot be

accomplished by generating adenoviruses comprising chimeric fibers without other capsid modifications.

Applicant's arguments filed 1/6/03 have been fully considered but they are not persuasive. Crystal does envision chimeric fibers that are derived from serotypes 1, 2, 3, 5, 6, 7, 11, 12, 14, 16, 21, 34, 35, 40 or 41 (column 4, line 32-41). The native fiber proteins are deleted of 1-50 to 1-700 amino acids. The tail region is not deleted in at least some of these deletions as the head region is about 100 amino acids. The inferiority of one of the disclosed Wickham fibers on altered antigenicity is of no consequence as the teachings of Wickham are that the tropism of the adenovirus can be swapped between adenovirus of different serotypes and that the head of the fiber is responsible for receptor binding. Nonetheless, Wickham envisions chimeric fibers that are formed from various serotypes. Given the teachings of Crystal et al, these serotypes can be utilized.

The MPEP states that "To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP § 2143 - § 2143.03 for decisions pertinent to each of these criteria" (MPEP 706.02(j). As taught by Wickham et al. chimeric fiber proteins can be generated by the substitution of regions

of one fiber protein for another. Crystal advances this art by the use of the fiber modifications for the express purpose of lowering antigenicity. The motivation to combine the reference teachings was to incorporate the benefit of altered tropism as detailed in Wickham et al in the chimeric fusion of Crystal that had reduced antigenicity.

Crystal teaches that switching the fiber from that of adenoviral serotype 5 to that of serotype 7 and the antigenicity of the resultant adenovirus is reduced by additional alterations in the hexon protein. However, the inventors envision altered antigenicity due to generation to chimeric fiber proteins in recombinant adenovirus as demonstrated by the scope of the claims. Claim 8 recites a chimeric adenovirus fiber, which has decreased ability or inability to be recognized by a neutralizing antibody directed against the wile-type adenovirus coat protein. That the Ad5/7 chimera is insufficient to allow the vector to escape neutralizing antibodies does not mean that the antigenicity is not reduced. Therefore, Crystal does not teach away from the instant invention. Also, instant claims have open claim language and encompass embodiments wherein other chimeric capsid proteins (e.g. hexons) with decreased antigenicity. Thus, Crystal et al. still read on the instant claims.

Dr. Havenga's Declaration of 1/6/03 teaches that the instant invention can be used to generate recombinant adenoviruses with desired antigenicity and tropism that are different from the antigenicity and tropism of the adenovirus from which the recombinant adenovirus is derived. Chimeric adenovirus designed according to the invention are not neutralized by antibodies in the serum of mice as illustrated by the luciferase activity detected following infection with wild type adenovirus versus recombinant adenovirus (as detailed in figures 2-4). Dr. Havenga also explains that the chimeric Ad5/Ad7 adenovirus of the Crystal patent differ

from those of the instant application in that 1) Ad7 fiber proteins used by Wickham et al. and Crystal et al. do not lead to differential targeting of the adenovirus 2) Ad5/Ad7 chimera are readily neutralized and 3) Ad5/Ad7 chimera are not stable. In the instant invention, adenovirus of the prior art are advanced by utilizing adenoviral fiber "parts" of Ad 11, 14, 16, 21, 34, 35 and 50 fused to the tail region of the native adenovirus thus diversifying the tropism and improving the stability of the recombinant adenovirus. Finally, as support for the instant claims, Dr. Havenga points to pages 32-41 of the specification as teachings "the retention of the native fiber tail region is accomplished by the method set forth at pages 32-34 of the specification of the present application and the generation of chimeric adenoviruses having part of the nonnative fibers fused to the tail region of the native fiber is set firth at pages 34-41 of the Specification."

The Declaration filed on 1/6/03 under 37 CFR 1.131 has been considered but is ineffective to overcome the 103(a) reference over Crystal et al. in view of Wickham et al. Dr. Havenga argues that an unexpected benefit of the instant invention is that recombinant adenoviruses with chimeric fiber proteins with a desired antigenicity and tropism different from the antigenicity and tropism of the native adenoviral serotype. While applicant wishes to distinguish itself from the Ad5/Ad7 chimeric adenovirus of Crystal et al., a comparison of an Ad5/Ad7 chimeric adenovirus to that of the instant invention is not a valid comparison. A more valid and direct comparison between the chimeric adenovirus of the instant invention and the combined teachings of Crystal et al and Wickham et al. result from following the teachings of Crystal et al. in view of Wickham to generate a recombinant adenovirus in which the native adenovirus is Ad5 and the nonnative fiber parts are from Ad35. The resultant chimeric Ad5/Ad35 adenovirus is of altered tropism and antigenicity, is well within the combined

teachings of Crystal et al. and Wickham et al. and would be indistinguishable form the chimeric adenovirus of the instantly claimed invention.

Furthermore, the instant invention wishes to distinguish itself from the invention of Crystal et al. in view of Wickham et al. by claiming chimeric fiber proteins that are generated by fusing a part of a fiber protein from an adenovirus of a second serotype to a **tail region** of a native fiber. The pages of the specification that are cited as support for these claims teaches that the sequences from 19 different serotypes of adenovirus were aligned to identify the conserved region in the tail and known regions. From the alignment, degenerative oligonucleotides were generated. Oligonucleotides used to amplify the fiber sequences are provided in table 3. The fiber DNA's were then amplified a, digested and inserted into pBr/AdBAMRΔΔFib. The disclosure as filed lacks support for the limitation that the tail region of the native fiber is fused to the part of the nonnative fibers.

No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (703) 605-1207. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (703) 305-1998. The fax phone numbers for

the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-3291.

Maria B Marvich, PhD
Examiner
Art Unit 1636

March 24, 2003

DAVID GUZO
PRIMARY EXAMINER